wherein the polypeptide monobody binds to a specific binding partner (SBP) to form a polypeptide:SBP complex.

2. **[Twice Amended]** The monobody of claim 1, wherein [the] at least one loop region binds to a specific binding partner (SBP) to form a polypeptide:SBP complex having a dissociation constant of less than 10^{-6} moles/liter.

4. **[Twice Amended]** The monobody of claim 1, wherein [the] a loop region comprises amino acid residues:

i) from 15 to 16 inclusive in an AB loop;

ii) from 22 to 30 inclusive in a BC loop;

iii) from 39 to 45 inclusive in a CD loop;

iv) from 51 to 55 inclusive in a DE loop;

v) from 60 to 66 inclusive in an EF loop; or

vi) from 76 to 87 inclusive in an FG loop.

5. **[Twice Amended]** The monobody of claim 1, wherein the monobody loop region sequence varies from the wild-type Fn3 loop region sequence by the deletion or replacement of [2 to 25] at least two to all the amino acids in the loop region.

REMARKS

The present invention relates to "artificial mini-antibodies" or "monobodies," *i.e.*, polypeptides made of Fn3 β-strand domains and one or more loop regions, where the monobodies are capable of binding to a variety of specific binding partners.

Applicant has carefully reviewed and considered the Office Action mailed on January 22, 2001, and the references cited therewith. Claims 1, 2, 4 and 5 are amended; claim 3 is canceled; as a result, claims 1, 2 and 4-6 are now pending in this application. No new subject matter has been added. The cancellations and amendments have been made to clarify the claims in order to expedite prosecution of the present application, and not for reasons of patentability. Therefore, the amendments are not intended to limit the scope of equivalents to which any claim element

may be entitled. The amendments to the claims are fully supported by the specification as originally filed.

Claim 1 has been amended to recite that at least one monobody loop region sequence has been varied as compared to the wild-type loop region sequence, where the loop region is linked between two Fn3 β-strand domain sequences. The phrase "at least two" and "plurality" synonymous in common patent usage. *See, e.g.*, Landis on Mechanics of Patent Claim Drafting (4th ed., PLI 1996) at page III-17 ("plurality . . . used for an indefinite number, two or more") (copy attached). Applicant is following this general practice of having "at least two" and "plurality" be synonymous. Support for the recitation of "at least two," therefore, is found throughout the specification, for example at page 6, lines 20 and 21; page 7, lines 8, 9, 19, 20 and 30; page 8, lines 6 and 7; page 9, lines 7-9; page 10, lines 18-20; and original claims 1, 11-15, 31 and 33.

Claim 1 has also been amended to recite that the variation in the loop(s) can be by deletion of at least two to all amino acids in the loop region sequence, insertion of at least two to 25 amino acids, or replacement of at least two to all the amino acids in the loop region sequence. The word "or" is used herein in conformance with common patent law practice in the conjunctive or disjunctive, *i.e.*, and/or. Support for the deletion of "at least two amino acids" is found in originally filed claims 1 and 5, and logic dictates that the upper limit may be no more than all of the amino acids in the loop. Support for the replacement of "at least two amino acids" is also found in originally filed claims 1 and 5, and again, logic dictates that the upper limit may be no more than all of the amino acids in the loop. The Examiner's attention is also drawn, for example, to Table 1 on page 21 and Table 5 on page 48 of the specification where many different combinations of deletions and/or replacements are depicted. It is, therefore, well within the ability of one having skill in the art, in conjunction with the teachings of the application, to make many different loop variants. Support for the insertion of "at least two" is found in originally filed claims 1 and 5, and support for "25 amino acids" is found in claim 6.

Claim 1 has also been amended to recite that the polypeptide monobody of the present invention binds to a specific binding partner (SBP) to form a polypeptide:SBP complex. Support for this amendment is found in claim 2, and throughout the specification (*e.g.*, page 28, line 18 through page 30, line 18; page 32, line 15 through page 33, line 25; page 43, line 7 through page

46, line 28; page 47 line 15 through page 49, line 28; and page 53, line 26 through page 57, line 20).

Claims 2, 4 and 5 have been amended so as to have proper antecedent basis in claim 1. These amendments are being made for formal reasons only, and therefore do not limit the scope of equivalents to which the claims are entitled.

Information Disclosure Statement

The Examiner states that paper #19 listed on the IDS of 7/47/01 was not previously provided. Enclosed is a Supplemental IDS including the full citation and a copy of this reference. Applicant requests that the Examiner initial the attached Form 1449.

§112 Rejection of the Claims

Claims 1-6 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled commensurate in scope with the specification. Claim 1 has been amended; insofar as the rejection is applied to the pending claims, it is hereby traversed.

Claim 1 has been amended to recite certain structural and functional elements of the monobody. In particular, at least one monobody loop region sequence varies (as compared to the wild-type loop region sequence) by deletion of at least two to all amino acids in the loop region sequence, insertion of at least two to 25 amino acids, or replacement of at least two to all the amino acids in the loop region sequence. Further, the polypeptide monobody binds to a specific binding partner (SBP) to form a polypeptide:SBP complex.

To the extent that the Examiner's statement is intended as support for an argument that claim 1 encompasses inoperative embodiments, the Examiner is requested to note that claims are in accord with the requirements of 35 U.S.C. § 112 if one of skill in the art, guided by the specification, could avoid inoperable combinations and practice the invention without undue experimentation. The mere possibility that a claim embraces inoperable embodiments does not render it unduly broad. In addition, it is not a function of the claims to specifically exclude all possible inoperative substances.

It should be noted that the present claims are not directed to a monobody that necessarily has the same protein folding/conformation as that of native Fn3, or a portion of Fn3 if not all of

the beta-strands are present. Instead, the claims recite a polypeptide monobody that has a certain structure (at least two Fn3 β-strand domain sequences with a loop region sequence linked between each Fn3 β-strand domain sequence, where the loop region has been modified by an insertion, deletion and/or replacement) and a certain function (binds to a specific binding partner (SBP) to form a polypeptide:SBP complex). The specification teaches appropriate tests to determine if the resulting monobodies have the claimed function of being able to bind to an SBP. *See, e.g.,* page 28, line 18 through page 30, line 18; page 32, line 15 through page 33, line 25; page 43, line 7 through page 46, line 28; page 47 line 15 through page 49, line 28; and page 53, line 26 through page 57, line 20. Compliance with 35 U.S.C. §112 must be adjudged from the perspective that claims are addressed to a person of average skill in the particular art, who would not choose a combination that would render a claimed composition inoperative. *Ex Parte Cole*, 223 U.S.P.Q. 94 at 95-96 (Bd. Pat. App. 1983) (copy enclosed). One skilled in the art in possession of the present specification could readily ascertain whether a compound comprising a given loop variation would be suitable for a certain SBP. Accordingly, the Examiner is respectfully requested to find the pending claims to be in compliance with 35 U.S.C. §112, first paragraph.

The January 22, 2001 Office Action at page 4, lines 1-2 states that the claims are not enabled because at least two Fn3 beta-strand domains would not be as stable as the entire Fn3 domain. The Examiner may, in fact, be correct that this smaller molecule may not be as stable. The claims, however, do not require such stability, but simply that the molecule has sufficient structure so as to give it the functionality of being able to bind to a specific binding partner (SBP) to form a polypeptide:SBP complex.

The Office Action states that one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention. Applicant asserts that the present patent specification teaches one skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. The present specification teaches the starting material for the monobody (*i.e.*, at least two Fn3 β-strand domain sequences with a modified loop region sequence linked

between each Fn3 β-strand domain sequence), and that the resulting polypeptide monobody binds to an SBP. Thus, the specification is enabling.

If the Examiner takes the view that the specification must not only indicate the starting material, but also teach how the modification in the loop region is to occur (*e.g.*, substitution, deletion, or insertion), then Applicant maintain that the specification is still enabling. Some experimentation would be needed in order to test all the possible new proteins that could be made and be covered by Applicant's application. The amount of experimentation, however, would not be undue in view of teaching of the specification. The factors to be considered under *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d (BNA) 1400, 1404 (Fed. Cir. 1988) in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification provides a significant amount of direction and guidance (**factor 2**), and that guidance is in the form of actual working examples (**factor 3**). Example VI teaches methods for making loop variegations in the FG and BC loop. Examples IX, X, XII , and XVI teach the selection of phage-displayed monobodies that bind to target molecules.
XII, and XVI teach the selection of phage-displayed monobodies that bind to target molecules.

Additional experiments were performed by the inventor that further support the pending claims. Declaration of Shohei Koide at ¶¶ 2-4. Mutant FNfn10 proteins that contain glycine insertions or glycine-rich insertions in the AB, BC, CD, DE, EF or FG loops were prepared and were functional. Also, non-glycine mutations were made in the AB loop that were functional in binding to their SBP. Declaration of Shohei Koide at ¶¶ 5-6.

The skill of those in the art (**factor 6**) is quite high in the fields of molecular biology and immunology, as evidenced by the level of sophistication of the experiments set forth in the specification. The state of the prior art (**factor 5**) with respect to what was known about Fn3 was well-developed.

Regarding the quantity of experimentation necessary (**factor 1**) and the predictability or unpredictability of the art (**factor 7**), mathematically a large number of monobody molecules

could be generated and screened. With respect to "undue experimentation," the fact that the outcome of a synthesis/screening program is unpredictable is precisely why a screening program is carried out. The Office simply cannot reasonably contend that a screening program to locate biomolecules with target biological properties would not be carried out by the art worker because the results cannot be fully predicted in advance. In fact, the Federal Circuit has explicitly recognized that a need to carry out extensive synthesis and screening programs to locate bioactive molecules does not constitute undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988). In *Wands* the court held that a process of immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics did not require undue experimentation. The Court stated:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Likewise, practitioners having skill in the art related to the present application, given the teachings of the present specification, would be well-equipped to prepare and screen polypeptide monobodies that bind to a specific binding partner. Thus, the fact that a claim may encompass a large number of polypeptide monobodies is not dispositive of the enablement issue. This is particularly true in an art area in which the level of skill is very high, and where the specification gives working examples on how to make various polypeptide monobodies (Examples I through VIII), and how to test a monobody's ability to bind to an SBP (Examples IX through XIV).

Considering all eight of the *Wands* factors, it clearly would not require undue experimentation to obtain polypeptide monobodies commensurate in scope with the pending claims. Appellants therefore assert that the specification fully enables one skilled in the art to construct polypeptide monobodies made of Fn3 β-strand domains and one or more loop regions, where the monobodies are capable of binding to a variety of specific binding partners.

The Examiner further states that claim 3 is not enabled. Applicant disagrees with the Examiner, but has cancelled claim 3 in order to expedite prosecution.

Applicant, therefore, requests that the rejections under 35 U.S.C. § 112 be withdrawn.

§103 Rejection of the Claims

Claims 1-6 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Main *et al.* (Cell 71:671-678, 1992, IDS #5) and further in view of Lee *et al.* (Protein Engineering 6:745-754, 1993, IDS #8).

Main *et al.* discuss the three-dimensional structure of the tenth type III module of fibronectin (FN3). They also determined that a functional RGD tri-peptide is located in the FG loop (Fig. 2), and that the loops bearing RGD motifs may be flexible, rather than existing in a specific conformation (p. 676). They compared the FNfn10 structure to other known structures and found it to be similar to immunoglobulin C domains. At the very end of the article, they also postulate that "the structure presented in this paper gives insight into the way a functional loop can be built onto a structural framework and, by virtue of its flexibility, be able to perform a wide range of functions." This mere invitation to experiment, or an "obviousness to try," however, has long been held not to constitute obviousness. *In re O'Farrell*, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988) (emphasis in original). This is especially true in view of the Examiner's enablement rejection discussed above. Main *et al.* do not teach or suggest whether it is possible to replace one or more loops of FN3 without detrimental effects on functionality of the molecule. Even if the article did provide motivation in general to vary the loop regions of an FNfn10 molecule, this does not necessarily make obvious a monobody containing a varied loop that can bind to a SBP.

Lee *et al.* do not remedy the deficiencies of Main *et al.* Lee *et al.* found that a short RGD sequence could be inserted into a "presentation scaffold." They found, however, that when a loop of REI V_L (an immunoglobulin domain) was replaced with an RGD sequence, the RGD sequence lost its biological function (page 751, Table I). Denaturation of the scaffold restored the RGD function, indicating that the restriction of the RGD conformation by these scaffolds had a detrimental effect on the function of the RGD sequence. Only when the RGD sequence was inserted in a loop of REI V_L with additional linker sequences was the resulting RGD-V_L hybrid protein functional (page 751, Table I). The loop was significantly longer than the parental one (10 and 14 residues in the hybrids versus 6 in the parental protein) (page 752, Figure 6). Despite their use of sophisticated molecular modeling methods, the interleukin-1β (IL-1β)-RGD hybrid

protein was inactive, demonstrating the difficulty in designing a biologically active loop (page 751, Table I).

Lee *et al.* mention that "fibronectin type III contains the RGD sequence in the last loop of a beta-rich fold suggested to be a member of the immunoglobulin superfamily" (page 753, left line 17; citation of Baron *et al.*). They also suggested that "one exciting application of presentation scaffolds is for conferring conformational constraints in the fusion phage approach to selection of high affinity peptide sequences" (page 753, left, line 38), and that "scaffolds capable of displaying more than one sequence might be used to construct multifunctional molecules as well as reconstruct discontinuous binding surfaces such a s those found in hormone receptor binding sites" (page 753, left, line 52). These statements, however, like the statement by Main *et al.* are also mere invitations to experiment. This article did not teach whether it was possible to identify novel biologically active sequences that could be successfully inserted into "presentation scaffolds." Further, they did not teach whether "presentation scaffolds" could tolerate extensive mutations in loops and retain binding function. Nor did they teach whether "presentation scaffolds" impose unfavorable structural contexts and inhibit the biological activity of an inserted sequence.

Moreover, the examiner states on page 7 of the Office Action mailed August 18, 2000:

> As stated in Helms et al. "It is generally believed that loop regions in globular proteins, and particularly hypervariable loops in immunoglobulins, can accommodate a wide variety of sequence changes without jeopardizing protein structure or stability. We show here, however, that novel sequences introduced within complementarity determining regions (CDRs) 1 and 3 of the immunoglobulin variable domain REI VL can significantly diminish the stability of the native state of this protein" (see abstract and entire document). As stated in the specification of the Fn3 monobody "has a fold similar to that of immunoglobulin domains" (see page 18, lines 20-21) and as such <u>one skilled in the art would reasonably conclude from Helms et al that not every loop replacement will result in a correctly folded protein wherein the loop region would bind to a specific binding partner</u>. (emphasis added)

In particular, it was not obvious whether loops other than the FG loop (that contains the functional RGD sequence in the 10th Fn3 domain) could accommodate novel amino acid sequences. Therefore, it appears that the examiner agrees that, although Lee *et al.* and Main *et al.* teach that FN3 is homologous to an immunoglobulin domain and that it may be possible to

use a presentation scaffold to display a functional peptide, one skilled in the art would reasonably conclude from Helms *et al.* that there was some uncertainty whether or not loop replacements could be made that would result in a varied loop region that can bind to a specific binding partner.

It has been demonstrated that the disulfide bond in the immunoglobulin domain is critical in maintaining its structure and stability (Goto and Hamaguchi, (1979) the role of the intrachain disulfide bond in the conformation and stability of the constant fragment of the immunoglobulin light chain, *J. Biochem.* 86:1433-1441). It is well known that disulfide bonds can stabilize a particular protein conformation by linking two cysteines that are distant along the polypeptide. Although the extensive experimental data on immunoglobulins have demonstrated that the immunoglobuin scaffold can accommodate numerous loop sequences, these immunoglobulin domains were stabilized by the critical disulfide bond. In contrast, the Fn3 scaffold does not contain disulfide bonds. The lack of stabilizing disulfide bonds makes it difficult to extrapolate the knowledge on immunoglobulins to the Fn3 scaffold and also makes it harder to predict the effects of loop mutations on the structure and stability of Fn3. Thus, one skilled in the art could not predict, without extensive experimentation, whether the Fn3 scaffold can be used as a "presentation scaffold."

Thus, it was not obvious *a priori* that the present inventor would be successful in making the claimed functional monobody until he actually performed the experiments. Applicant submits that it would require the impermissible application of hindsight to arrive at the claimed subject matter given the cited art. Such a use of hindsight is improper when resolving the question of obviousness. The direction must be provided by the art, not by the disclosure of the present specification.

Further, a number of research groups have sought ligands specific for various proteins. The work described by Twan van den Beucken *et al.* in the *Journal of Molecular Biology* (2001) **310**, 591-601 is illustrative. In this work, the authors state that "ligands specific for B7.1 (CD80) and B7.2 (CD86) have applications in disease indications that require inhibition of T-cell activity. As we observed significant sequence and structural similarity between the B7-binding ligand, cytotoxic T-lymphocyte associated protein-4 (CTLA-4), and antibody variable light chain

domains (VLs), we have explored the possibilities of making novel B7 binding molecules based on single VL domains." (p. 591, beginning of the Abstract)

The investigators in the van den Beucken *et al.* paper described their rationale for what molecule to use that would bind to B7. Their discussion illustrates that there were not a large number of protein scaffolds that would perform the desired function. In particular, they stated that "[i]n order to find protein frameworks with a similar structure onto which we could potentially graft functional fragments from CTLA-4, we performed a BLAST protein sequence-similarity search with human CTLA-4." ("Results" p. 592, col. 2) The scientists expected that it would be necessary to use a framework similar to that of CTLA-4 to correctly display the "functional fragments." They continued by stating that the "conclusion of this analysis was that despite the generally low degree of amino acid sequence similarity and the enormous conformational variability of the loops, the beta-sheets forming the framework were remarkably similar between most VL domains and CTLA-4. From this we reasoned that it should be possible to take one of these VL domains and graft on the CDR-like loops from CTLA-4 at structurally compatible sites." Were other frameworks obvious, it is unclear why they would have gone to this trouble.

Initially this seemed like a good line of reasoning in order to produce a B7 binder. This, however, was not the result. The authors went on to state that a "chimeric VL/CTLA-4 gene was constructed and cloned for expression and display. Low levels of soluble protein product were detected by Western blotting (Figure 1(c), lane 3) which suggested that this molecule was folded and could be secreted from *Escherichia coli*. However, no binding of the phage-displayed or soluble protein to the natural ligands B7.1 and B7.2 was observed (data not shown)." (page 592 end to page 593 top, emphasis added)

So, even using a framework that could reasonably be considered optimal, their efforts were not successful. Thus it took even these highly skilled practitioners in the art multiple attempts before they could generate scaffolds that could be used to display "CDR-like" loops and result in the B7 ligand binders that they sought. Of course, the authors were eventually successful, but this was only after preparing diverse libraries of VL frameworks and further applying *in vitro* mutagenesis. Negative results, such as those above, are not typically reported in the literature, except in the context of a subsequent success. It is possible, however, to see the

outlines of a significant problem in the art, for which there was no obvious solution, by looking at the obstacles that some very highly skilled practitioners had to overcome in order to achieve what the present invention provides so plainly and elegantly.

Another example of this is seen in the work of Desiderio *et al.* entitled, "A Semi-synthetic Repertoire of Intrinsically Stable Antibody Fragments Derived from a Single-framework Scaffold" (*Journal of Molecular Biology* (2001) **310**, 603-615). This group, in the first sentence of their Abstract, p. 603, reports, "the design, construction and use of an antibody bacteriophage display library built on the scaffold of a single-chain variable fragment (scFv) previously proven to be functionally expressed in the reducing environment of both bacterial and plant cytoplasm and endowed with intrinsic high thermodynamic stability."

These authors comment (p. 604, col. 1) that "the use of phage display does not always ensure a selection of molecules endowed with excellent folding properties, high yields or stability. These properties are especially desirable when antibody fragments must be expressed in cellular environments that are incompatible with disulphide bond formation, such as in the reducing conditions of the cytoplasm. There is great interest in the ability to express functional intracellular antibodies (intrabodies) in this compartment for their potential immunotherapeutic use." Thus, numerous scaffolds with such properties were not common or obvious. The insight of their use of this particular antibody (a single-chain Fv fragment here) is useful, interesting, and highly publishable because obvious alternatives did not exist.

The Desiderio *et al.* authors took pains to use to antibodies as their scaffold. In fact, the scaffold that they used for this application was first published in 1993. They used an antibody scaffold because skilled practitioners knew that antibodies could provide a scaffold on which to make modifications and libraries of modifications. If it were obvious to use other scaffolds, and obvious that such scaffolds would work, there would have been little point to what they did here.

In their Discussion section on p.609 (col. 1), the Desiderio *et al.* scientists state, "Therefore, for applications that require a specific interference to cytoplasmic-related functions, it is fundamental to search for antibodies that can fold in the absence of disulphide bonds." A "search" would not be necessary if such scaffolds were "obvious." Further, their search would not have been limited to "antibodies" if it was obvious that other proteins would also work.

It should be noted that the claimed monobody scaffolds fully comply with the requirements stated by these authors. Monobodies do not have disulfide bonds. They readily fold and exhibit stabilities at temperatures of up to about 70° C or more, in some cases. They are soluble and can be produced at high levels in *E. coli.* In addition, the Desiderio *et al.* molecules, should they have retained any of the non-human character of their origin, would be distinctly inferior to the claimed human fibronectin-derived scaffold, because of their likely antigenicity in humans.

Finally, if it were obvious that other proteins could provide useful scaffolds, then certainly the first one that anyone would want to try would be a protein designed by nature to have a variable portion *in vivo* for the exact purpose of binding to and displaying small peptides, such as the T-cell receptor. In fact, numerous groups have worked with this molecule with the intent of harnessing it as a scaffold. The history of these efforts is best summarized by Shusta, *et al.* in their paper entitled, "Directed evolution of a stable scaffold for T-cell engineering" (Nature Biotechnology (2000) **18**, 754-759).

In the opening paragraph of their paper they state that although the diversity of TCRs is similar to that of antibodies, soluble TCRs have not yet been exploited in immunotherapeutical strategies with the potential to provide highly antigen-specific immunosuppression. They continue by stating that "such applications have not been realized for various reasons. Affinities of TCR/pMHC interactions are quite low (micromolar Kd), necessitating unfeasibly high concentrations of soluble TCR for targeting. Many TCRs have low solubility and a high propensity to aggregate, which is improve somewhat by fusion of the TCR variable regions to thioredoxin or antibody constant regions. Stability of soluble TCRs are low compared to antibodies, and recombinant production yields are low and variable."

The authors continue by stating the properties that would be desirable. Their paper further reports their own temperature-based screening system that allowed them to arrive at a relatively stable, soluble, single-chain T-cell receptor scaffold. Their methodology and the product produced were certainly not obvious. One might object that this is just an isolated case of the TCR being a problem. If this is the case, then there still was no guidance for what other proteins would be useful as scaffolds without such an arduous process of experimentation and testing.

One of the interesting conclusions of the Shusta *et al.* authors was that there is a relationship between stability and improved display. They state in their final paragraph on page 758, "We had previously observed that well-displayed mutant scTCRs are more stable. In the present work, this connection has been strengthened by the observation that selection for increased stability in turn results in improved display (Fig. 1D,F). These findings suggest that in the case of the scTCR, the efficiency of the complex kinetic process of in vivo protein folding can be predicted with a single thermodynamic parameter, the in vitro stability of the protein (and vice versa). The robustness of this correlation gives confidence that this approach may be of general utility for obtaining stable scaffolds in other areas of protein engineering." (emphasis added)

In conclusion, it is evident from the literature that, rather than the present scaffolds being obvious, they instead are quite non-obvious and require extensive experimentation (that is not always successful) in order to be established. Accordingly, Applicant respectfully requests withdrawal of this 35 U.S.C. § 103(a) rejection of the of the claims.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612 373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

SHOHEI KOIDE

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Box AF, Commissioner of Patents, Washington, D.C. 20231, on this 25 day of October, 2001.

Candis B. Buending
Name

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Signature